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THE UNITED STATES OF AMERICA

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United States Patent and Trademark Office

December 17, 2004

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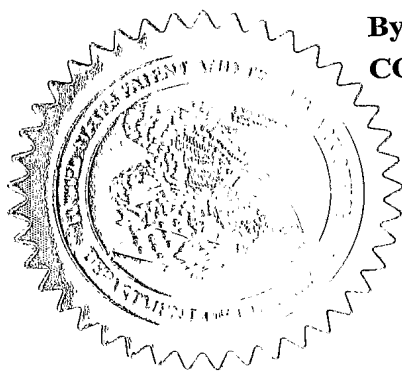
APPLICATION NUMBER: 60/540,307

FILING DATE: January 28, 2004

PRIORITY DOCUMENT

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COMPLIANCE WITH RULE 17.1(a) OR (b)**

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Lanai Jamison

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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

Express Mail Label No. _____

22151 U.S. PTO
60/540307

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Additional inventors are being named on the <u>1</u> separately numbered sheets attached hereto					
TITLE OF THE INVENTION (500 characters max)					
A CRYSTALLINE FORM OF 1-(((1(R)-(3-(2-(7-CHLORO-2-QUINOLINYL)ETHENYL)-PHENYL)-3-(2-(1-HYDROXY-1-METHYLETHYL) PHENYL) PROPYL) THIO) METHYL) CYCLOPROPANE ACETIC ACID					
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ENCLOSED APPLICATION PARTS (check all that apply)					
<input checked="" type="checkbox"/> Specification Number of Pages		16		<input type="checkbox"/> CD(s), Number _____	
<input type="checkbox"/> Drawing(s) Number of Sheets		3		<input type="checkbox"/> Other _____	
<input checked="" type="checkbox"/> Application Data Sheet. See 37 CFR 1.76		(specify): _____			
METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT					
<input type="checkbox"/> Applicant claims small entity status. See 37 CFR 1.27.				FILING FEE AMOUNT (\$)	
<input checked="" type="checkbox"/> A check or money order is enclosed to cover the filing fees.				160.00	
<input checked="" type="checkbox"/> The Director is hereby authorized to charge filing fees or credit any overpayment to Deposit Account Number: 04-0100					
<input type="checkbox"/> Payment by credit card. Form PTO-2038 is attached.					
The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.					
<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes, the name of the U.S. Government agency and the Government contract number are: _____					

[Page 1 of 2]

Respectfully submitted,

Date January 28, 2004

SIGNATURE
TYPED OR
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REGISTRATION NO.
(if appropriate)

25,351

Docket Number:

03818/0200780-US0

USE ONLY FOR FILING A PROVISIONAL APPLICATION FOR PATENT

Express Mail Label No.

Dated: _____

PROVISIONAL APPLICATION COVER SHEET
Additional Page

PTO/SB/16 (08-03)

Approved for use through 07/31/06. OMB 0651-0032

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Docket Number 03818/0200780-USO		
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[Page 2 of 2]

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**FEE TRANSMITTAL
for FY 2004**

Effective 10/01/2003, Patent fees are subject to annual revision.

☐ Applicant claims small entity status. See 37 CFR 1.27**Compleat if Known**

Application Number	Not Yet Assigned
Filing Date	Concurrently Herewith
First Named Inventor	Michaela Horvat
Examiner Name	Not Yet Assigned
Art Unit	N/A
Attorney Docket No.	03818/0200780-USO

TOTAL AMOUNT OF PAYMENT (\$) 160.00**METHOD OF PAYMENT (check all that apply)**☒ Check ☐ Credit Card ☐ Money Order ☐ Other ☐ None☐ Deposit Account:Deposit
Account
Number

04-0100

Deposit
Account
Name

Darby & Darby P.C.

The Director is authorized to: (check all that apply)

☐ Charge fee(s) indicated below ☒ Credit any overpayments☐ Charge any additional fee(s) or any underpayment of fee(s)☐ Charge fee(s) indicated below, except for the filing fee
to the above-identified deposit account.**FEE CALCULATION****1. BASIC FILING FEE**

Large Entity		Small Entity		Fee Description	Fee Paid
Fee Code	Fee (\$)	Fee Code	Fee (\$)		
1001	770	2001	385	Utility filing fee	
1002	340	2002	170	Design filing fee	
1003	530	2003	265	Plant filing fee	
1004	770	2004	385	Reissue filing fee	
1005	160	2005	80	Provisional filing fee	160.00

SUBTOTAL (1) (\$) 160.00**2. EXTRA CLAIM FEES FOR UTILITY AND REISSUE**

Total Claims	Extra Claims	Fee from below	Fee Paid
16	** =	x	=
3	** =	x	=
Multiple Dependent			

Large Entity		Small Entity		Fee Description	Fee Paid
Fee Code	Fee (\$)	Fee Code	Fee (\$)		
1202	18	2202	9	Claims in excess of 20	
1201	86	2201	43	Independent claims in excess of 3	
1203	290	2203	145	Multiple dependent claim, if not paid	
1204	86	2204	43	** Reissue independent claims over original patent	
1205	18	2205	9	** Reissue claims in excess of 20 and over original patent	

SUBTOTAL (2) (\$) 0.00

**or number previously paid, if greater; For Reissues, see above

FEE CALCULATION (continued)**3. ADDITIONAL FEES**

Large Entity		Small Entity		Fee Description	Fee Paid
Fee Code	Fee (\$)	Fee Code	Fee (\$)		
1051	130	2051	65	Surcharge - late filing fee or oath	
1052	50	2052	25	Surcharge - late provisional filing fee or cover sheet.	
1053	130	1053	130	Non-English specification	
1812	2,520	1812	2,520	For filing a request for ex parte reexamination	
1804	920*	1804	920*	Requesting publication of SIR prior to Examiner action	
1805	1,840*	1805	1,840*	Requesting publication of SIR after Examiner action	
1251	110	2251	55	Extension for reply within first month	
1252	420	2252	210	Extension for reply within second month	
1253	950	2253	475	Extension for reply within third month	
1254	1,480	2254	740	Extension for reply within fourth month	
1255	2,010	2255	1,005	Extension for reply within fifth month	
1401	330	2401	165	Notice of Appeal	
1402	330	2402	165	Filing a brief in support of an appeal	
1403	290	2403	145	Request for oral hearing	
1451	1,510	1451	1,510	Petition to institute a public use proceeding	
1452	110	2452	55	Petition to revive - unavoidable	
1453	1,330	2453	665	Petition to revive - unintentional	
1501	1,330	2501	665	Utility issue fee (or reissue)	
1502	480	2502	240	Design issue fee	
1503	640	2503	320	Plant issue fee	
1460	130	1460	130	Petitions to the Commissioner	
1807	50	1807	50	Processing fee under 37 CFR 1.17(q)	
1806	180	1806	180	Submission of Information Disclosure Stmt	
8021	40	8021	40	Recording each patent assignment per property (times number of properties)	
1809	770	2809	385	Filing a submission after final rejection (37 CFR 1.129(a))	
1810	770	2810	385	For each additional invention to be examined (37CFR 1.129(b))	
1801	770	2801	385	Request for Continued Examination (RCE)	
1802	900	1802	900	Request for expedited examination of a design application	

Other fee (specify)

*Reduced by Basic Filing Fee Paid

SUBTOTAL (3) (\$) 0.00**SUBMITTED BY**

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Application No. (if known):

Attorney Docket No.: 03818/0200780-US0

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Provisional Patent Application Transmittal (2 pages)
Fee Transmittal (1 page)
Application Data Sheet (3 pages)
Specification, Claims and Abstract (16 pages)
3 sheet of drawings (Figs. 1-3)
Check No. 4002 in the amount of \$160.00

Application Data Sheet

Application Information

Application Type::	Provisional
Subject Matter::	Utility
Suggested Group Art Unit::	N/A
CD-ROM or CD-R?::	None
Sequence submission?::	None
Computer Readable Form (CRF)?::	No
Title::	A CRYSTALLINE FORM OF 1-(((1(R)-(3-(2-(7-CHLORO-2-QUINOLINYL)ETHENYL)-PHENYL)-3-(2-(1-HYDROXY-1-METHYLETHYL) PHENYL) PROPYL) THIO) METHYL) CYCLOPROPANE ACETIC ACID
Attorney Docket Number::	03818/0200780-US0
Request for Early Publication?::	No
Request for Non-Publication?::	No
Small Entity?::	No
Petition included?::	No
Secrecy Order in Parent Appl.?::	No

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EXPRESS MAIL CERTIFICATE

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5 A CRYSTALLINE FORM OF 1-(((1(R)-(3-(2-(7-CHLORO-2-QUINOLINYL)ETHENYL)-
PHENYL)-3-(2-(1-HYDROXY-1-METHYLETHYL)PHENYL)PROPYL)
THIO)METHYL) CYCLOPROPANE ACETIC ACID

Field of the Invention

10 The present invention relates to a new crystalline form of 1-(((1(R)-(3-(2-(7-chloro-2-quinoliny)ethenyl)-phenyl)-3-(2-(1-hydroxy-1-methylethyl)phenyl)propyl)thio)methyl)cyclopropane acetic acid, to a process for its preparation, to pharmaceutical formulations containing it, and to a method of treatment using the same.

15 Background of the Invention

The sodium salt of 1-(((1(R)-(3-(2-(7-chloro-2-quinoliny)ethenyl)-phenyl)-3-(2-(1-hydroxy-1-methylethyl)phenyl)propyl)thio)methyl)cyclopropane acetic acid (Montelukast sodium) is a therapeutic agent useful for the treatment of bronchial asthma. Montelukast sodium is disclosed in European Patent Application No. 480,717.

{W:\03818\0200780us0\00125423.DOC 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 }

Figure 3 shows a differential scanning calorimetry (DSC) thermogram of the crystalline form of 1-(((1(R)-3-(2-(7-chloro-2-quinolinyl)ethenyl)-phenyl)-3-(2-(1-hydroxy-1-methylethyl) phenyl)propyl)thio) methyl)cyclopropane acetic acid of the present invention.

5

Detailed Description of the Invention

A new crystalline form of 1-(((1(R)-3-(2-(7-chloro-2-quinolinyl)ethenyl)-phenyl)-3-(2-(1-hydroxy-1-methylethyl)phenyl)propyl)thio)methyl)cyclopropane acetic acid can be prepared by recrystallization of 1-(((1(R)-3-(2-(7-chloro-2-quinolinyl)ethenyl)-phenyl)-3-(2-(1-hydroxy-1-methylethyl)phenyl)propyl)thio)methyl)cyclopropane acetic acid from a mixture
10 of one or more aqueous buffers and acetone.

The starting material used to prepare the new crystalline form may be any amorphous or crystalline form of 1-(((1(R)-3-(2-(7-chloro-2-quinolinyl)ethenyl)-phenyl)-3-(2-(1-hydroxy-1-methylethyl) phenyl)propyl)thio)methyl)cyclopropane acetic acid, or any salt
15 thereof.

For the recrystallization, the pH range of the aqueous buffer is typically between about 2 and about 8, preferably from about 3 to about 7, and most preferably from about 4 to about 6. The ratio of aqueous buffer to acetone used in the recrystallization is typically from about 1:10 to about 10:1, preferably from about 1:4 to about 4:1, and most preferably from
20 about 1:2 to about 2:1. The recrystallization temperature is typically between about 5 °C and about 50 °C, preferably from about 10 °C to about 40 °C, and most preferably from about 20 °C to about 30 °C.

10

TABLE 1. Crystallographic data for the new crystalline form of 1-(((1*R*)-(3-(2-(7-chloro-2-quinolinyl)ethenyl)-phenyl)-3-(2-(1-hydroxy-1-methylethyl)phenyl)propyl)thio)methyl)cyclopropane acetic acid

15

{W:\03818\0200780us0\00125423.DOC { 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100 101 102 103 104 105 106 107 108 109 110 111 112 113 114 115 116 117 118 119 120 121 122 123 124 125 126 127 128 129 130 131 132 133 134 135 136 137 138 139 140 141 142 143 144 145 146 147 148 149 150 151 152 153 154 155 156 157 158 159 160 161 162 163 164 165 166 167 168 169 170 171 172 173 174 175 176 177 178 179 180 181 182 183 184 185 186 187 188 189 190 191 192 193 194 195 196 197 198 199 200 201 202 203 204 205 206 207 208 209 210 211 212 213 214 215 216 217 218 219 220 221 222 223 224 225 226 227 228 229 230 231 232 233 234 235 236 237 238 239 240 241 242 243 244 245 246 247 248 249 250 251 252 253 254 255 256 257 258 259 260 261 262 263 264 265 266 267 268 269 270 271 272 273 274 275 276 277 278 279 280 281 282 283 284 285 286 287 288 289 290 291 292 293 294 295 296 297 298 299 300 301 302 303 304 305 306 307 308 309 310 311 312 313 314 315 316 317 318 319 320 321 322 323 324 325 326 327 328 329 330 331 332 333 334 335 336 337 338 339 340 341 342 343 344 345 346 347 348 349 350 351 352 353 354 355 356 357 358 359 360 361 362 363 364 365 366 367 368 369 370 371 372 373 374 375 376 377 378 379 380 381 382 383 384 385 386 387 388 389 390 391 392 393 394 395 396 397 398 399 400 401 402 403 404 405 406 407 408 409 410 411 412 413 414 415 416 417 418 419 420 421 422 423 424 425 426 427 428 429 430 431 432 433 434 435 436 437 438 439 440 441 442 443 444 445 446 447 448 449 450 451 452 453 454 455 456 457 458 459 460 461 462 463 464 465 466 467 468 469 470 471 472 473 474 475 476 477 478 479 480 481 482 483 484 485 486 487 488 489 490 491 492 493 494 495 496 497 498 499 500 501 502 503 504 505 506 507 508 509 510 511 512 513 514 515 516 517 518 519 520 521 522 523 524 525 526 527 528 529 530 531 532 533 534 535 536 537 538 539 540 541 542 543 544 545 546 547 548 549 550 551 552 553 554 555 556 557 558 559 560 561 562 563 564 565 566 567 568 569 570 571 572 573 574 575 576 577 578 579 580 581 582 583 584 585 586 587 588 589 590 591 592 593 594 595 596 597 598 599 600 601 602 603 604 605 606 607 608 609 610 611 612 613 614 615 616 617 618 619 620 621 622 623 624 625 626 627 628 629 630 631 632 633 634 635 636 637 638 639 640 641 642 643 644 645 646 647 648 649 650 651 652 653 654 655 656 657 658 659 660 661 662 663 664 665 666 667 668 669 670 671 672 673 674 675 676 677 678 679 680 681 682 683 684 685 686 687 688 689 690 691 692 693 694 695 696 697 698 699 700 701 702 703 704 705 706 707 708 709 710 711 712 713 714 715 716 717 718 719 720 721 722 723 724 725 726 727 728 729 730 731 732 733 734 735 736 737 738 739 740 741 742 743 744 745 746 747 748 749 750 751 752 753 754 755 756 757 758 759 760 761 762 763 764 765 766 767 768 769 770 771 772 773 774 775 776 777 778 779 780 781 782 783 784 785 786 787 788 789 790 791 792 793 794 795 796 797 798 799 800 801 802 803 804 805 806 807 808 809 810 811 812 813 814 815 816 817 818 819 820 821 822 823 824 825 826 827 828 829 830 831 832 833 834 835 836 837 838 839 840 841 842 843 844 845 846 847 848 849 850 851 852 853 854 855 856 857 858 859 860 861 862 863 864 865 866 867 868 869 870 871 872 873 874 875 876 877 878 879 880 881 882 883 884 885 886 887 888 889 890 891 892 893 894 895 896 897 898 899 900 901 902 903 904 905 906 907 908 909 910 911 912 913 914 915 916 917 918 919 920 921 922 923 924 925 926 927 928 929 930 931 932 933 934 935 936 937 938 939 940 941 942 943 944 945 946 947 948 949 950 951 952 953 954 955 956 957 958 959 960 961 962 963 964 965 966 967 968 969 970 971 972 973 974 975 976 977 978 979 980 981 982 983 984 985 986 987 988 989 990 991 992 993 994 995 996 997 998 999 1000 1001 1002 1003 1004 1005 1006 1007 1008 1009 1010 1011 1012 1013 1014 1015 1016 1017 1018 1019 1020 1021 1022 1023 1024 1025 1026 1027 1028 1029 1030 1031 1032 1033 1034 1

follows; $6.5 \pm 0.2^\circ$, $10.0 \pm 0.2^\circ$, $15.5 \pm 0.2^\circ$, $18.3 \pm 0.2^\circ$, $20.4 \pm 0.2^\circ$, $24.6 \pm 0.2^\circ$, measured using CuK α radiation on a powder sample collected using a Philips X'PertPRO powder diffractometer. This is shown in Figure 1.

5 Figures 2 and 3 show the Differential Scanning Calorimetry thermogram (DSC) and Infrared spectrum (IR), respectively, of the new crystalline form of 1-(((1(R)-(3-(2-(7-chloro-2-quinoliny)ethenyl)-phenyl)-3-(2-(1-hydroxy-1-methylethyl)phenyl)propyl)thio)methyl) cyclopropane acetic acid of the present invention. In the IR (Figure 2), characteristic bands are observed at $1715 \pm 5 \text{ cm}^{-1}$ and $3573 \pm 5 \text{ cm}^{-1}$. In the DSC (Figure 3), a characteristic endothermic
10 peak in range from 120°C to 180°C is observed.

 The purity of the solid new crystalline form of 1-(((1(R)-(3-(2-(7-chloro-2-quinoliny)ethenyl)-phenyl)-3-(2-(1-hydroxy-1-methylethyl)phenyl)propyl)thio)methyl) cyclopropane acetic acid obtained using the process of the present invention is typically greater than about 90.0 %, preferably greater than about 95.0 %, more preferably greater than about
15 99.0 % and the most preferably greater than about 99.9 %.

Therapeutic Formulations and Regimens

 The new crystalline form of 1-(((1(R)-(3-(2-(7-chloro-2-quinoliny)ethenyl)-phenyl)-3-(2-(1-hydroxy-1-methylethyl)phenyl)propyl)thio)methyl) cyclopropane acetic acid of
20 the present invention can be utilized in the preparation of rapid, controlled and sustained release pharmaceutical formulations, suitable for oral, rectal, parenteral, transdermal, buccal,

nasal, sublingual, subcutaneous or intravenous administration. Such formulations may be useful for the treatment of asthma in a human.

The formulations are preferably administered orally, in the form of rapid or controlled release tablets, microparticles, mini tablets, capsules and oral solutions or suspensions, or powders for the preparation thereof. In addition to the new crystalline form of 1-(((1(R)-(3-(2-(7-chloro-2-quinolinyl)ethenyl)-phenyl)-3-(2-(1-hydroxy-1-methylethyl)phenyl)propyl)thio) methyl) cyclopropane acetic acid of the present invention as the active substance, oral preparations may optionally include various standard pharmaceutical carriers and excipients, such as binders, fillers, buffers, lubricants, glidants, disintegrants, odorants, sweeteners, surfactants and coatings. Some excipients may have multiple roles in the formulations, e. g., act as both binders and disintegrants.

Examples of pharmaceutically acceptable disintegrants for oral formulations useful in the present invention include, but are not limited to, starch, pre-gelatinized starch, sodium starch glycolate, sodium carboxymethylcellulose, croscarmellose sodium, microcrystalline cellulose, alginates, resins, surfactants, effervescent compositions, aqueous aluminum silicates and crosslinked polyvinylpyrrolidone.

Examples of pharmaceutically acceptable binders for oral formulations useful herein include, but are not limited to, acacia; cellulose derivatives, such as methylcellulose, carboxymethylcellulose, hydroxypropylmethylcellulose, hydroxypropylcellulose or hydroxyethylcellulose; gelatin, glucose, dextrose, xylitol, polymethacrylates, polyvinylpyrrolidone, sorbitol, starch, pre-gelatinized starch, tragacanth, xanthane resin, alginates, magnesium-aluminum silicate, polyethylene glycol or bentonite.

Examples of pharmaceutically acceptable fillers for oral formulations include, but are not limited to, lactose, anhydrolactose, lactose monohydrate, sucrose, dextrose, mannitol, sorbitol, starch, cellulose (particularly microcrystalline cellulose), dihydro- or anhydro-calcium phosphate, calcium carbonate and calcium sulfate.

- 5 Examples of pharmaceutically acceptable lubricants useful in the formulations of the invention include, but are not limited to, magnesium stearate, talc, polyethylene glycol, polymers of ethylene oxide, sodium lauryl sulfate, magnesium lauryl sulfate, sodium oleate, sodium stearyl fumarate, DL-leucine and colloidal silicon dioxide

- 10 Examples of suitable pharmaceutically acceptable odorants for the oral formulations include, but are not limited to, synthetic aromas and natural aromatic oils such as extracts of oils, flowers, fruits and combinations thereof. Preferable are vanilla and fruit aromas, including banana, apple, sour cherry, peach and similar aromas. Their use depends on many factors, the most important being the organoleptic acceptability for the population that will be taking the pharmaceutical formulations.

- 15 Examples of suitable pharmaceutically acceptable dyes for the oral formulations include, but are not limited to, synthetic and natural dyes such as titanium dioxide, beta-carotene and extracts of grapefruit peel.

- 20 Examples of useful pharmaceutically acceptable coatings for the oral formulations, typically used to facilitate swallowing, modify the release properties, improve the appearance, and/or mask the taste of the formulations include, but are not limited to, hydroxypropylmethylcellulose, hydroxypropylcellulose and acrylate-methacrylate copolymers.

Suitable examples of pharmaceutically acceptable sweeteners for the oral formulations include, but are not limited to, aspartame, saccharin, saccharin sodium, sodium cyclamate, xylitol, mannitol, sorbitol, lactose and sucrose.

5 Suitable examples of pharmaceutically acceptable buffers include, but are not limited to, citric acid, sodium citrate, sodium bicarbonate, dibasic sodium phosphate, magnesium oxide, calcium carbonate and magnesium hydroxide.

Suitable examples of pharmaceutically acceptable surfactants include, but are not limited to, sodium lauryl sulfate and polysorbates.

10 Formulations of the new crystalline form of 1-(((1(R)-(3-(2-(7-chloro-2-quinolinyl)ethenyl)-phenyl)-3-(2-(1-hydroxy-1-methylethyl)phenyl)propyl)thio)methyl)cyclopropane acetic acid of the present invention can also be administered intravenously or intraperitoneally, by infusion or injection. Dispersions can also be prepared in a liquid carrier or intermediate, such as glycerin, liquid polyethylene glycols, triacetin oils, and mixtures thereof. To improve storage stability, such preparations may also contain a preservative to
15 prevent the growth of microorganisms.

Pharmaceutical formulations suitable for injection or infusion may be in the form of a sterile aqueous solution, a dispersion or a sterile powder that contains the active ingredient, adjusted, if necessary, for preparation of such a sterile solution or dispersion suitable for infusion or injection. This may optionally be encapsulated into liposomes. In all
20 cases, the final preparation must be sterile, liquid, and stable under production and storage conditions.

The liquid carrier or intermediate can be a solvent or liquid dispersive medium that contains, for example, water, ethanol, a polyol (e. g. glycerol, propylene glycol or the like), vegetable oils, non-toxic glycerine esters and suitable mixtures thereof. Suitable flowability may be maintained, by generation of liposomes, administration of a suitable particle
 5 size in the case of dispersions, or by the addition of surfactants. Prevention of the action of micro-organisms can be achieved by the addition of various antibacterial and antifungal agents, e. g. paraben, chlorobutanol, or sorbic acid. In many cases isotonic substances are recommended, e. g. sugars, buffers and sodium chloride to assure osmotic pressure similar to those of body fluids, particularly blood. Prolonged absorption of such injectable mixtures can
 10 be achieved by introduction of absorption-delaying agents, such as aluminium monostearate or gelatin.

Sterile injectable solutions can be prepared by mixing the new crystalline form of 1-(((1(R)-(3-(2-(7-chloro-2-quinoliny)ethenyl)-phenyl)-3-(2-(1-hydroxy-1-methylethyl)phenyl)propyl) thio)methyl) cyclopropane acetic acid with an appropriate solvent and one or
 15 more of the aforementioned excipients, followed by sterile filtering. In the case of sterile powders suitable for use in the preparation of sterile injectable solutions, preferable preparation methods include drying in vacuum and lyophilization, which provide powdery mixtures of the isostructural pseudopolymorphs and desired excipients for subsequent preparation of sterile solutions.

20 The compound of the present invention may also be used for the preparation of locally acting, topical formulations. Such formulations may also contain other pharmaceutically

acceptable excipients, such as polymers, oils, liquid carriers, surfactants, buffers, preservatives, stabilizers, antioxidants, moisturizers, emollients, colorants and odorants.

Examples of pharmaceutically acceptable polymers suitable for such topical formulations include, but are not limited to, acrylic polymers; cellulose derivatives, such as
5 carboxymethylcellulose sodium, methylcellulose or hydroxypropylcellulose; natural polymers, such as alginates, tragacanth, pectin, xanthan and cytosan.

Examples of suitable pharmaceutically acceptable oils which are so useful include but are not limited to, mineral oils, silicone oils, fatty acids, alcohols, and glycols.

Examples of suitable pharmaceutically acceptable liquid carriers include, but are not limited to,
10 water, alcohols or glycols such as ethanol, isopropanol, propylene glycol, hexylene glycol, glycerol and polyethylene glycol, or mixtures thereof in which the new crystalline form of 1-(((1(R)-(3-(2-(7-chloro-2-quinoliny)ethenyl)-phenyl)-3-(2-(1-hydroxy-1-methylethyl)phenyl)propyl)thio)methyl) cyclopropane acetic acid is dissolved or dispersed, optionally with the addition of non-toxic anionic, cationic or non-ionic surfactants, and inorganic or organic
15 buffers.

Suitable examples of pharmaceutically acceptable preservatives include, but are not limited to, various antibacterial and antifungal agents such as solvents, for example ethanol, propylene glycol, benzyl alcohol, chlorobutanol, quaternary ammonium salts, and parabens (such as methyl paraben, ethyl paraben, propyl paraben, etc.).

20 Suitable examples of pharmaceutically acceptable stabilizers and antioxidants include, but are not limited to, ethylenediaminetetraacetic acid (EDTA), thiourea, tocopherol and butyl hydroxyanisole.

Suitable examples of pharmaceutically acceptable moisturizers include, but are not limited to, glycerine, sorbitol, urea and polyethylene glycol.

Suitable examples of pharmaceutically acceptable emollients include, but are not limited to, mineral oils, isopropyl myristate, and isopropyl palmitate.

5 The use of dyes and odorants in topical formulations of the present invention depends on many factors of which the most important is organoleptic acceptability to the population that will be using the pharmaceutical formulations.

 The therapeutically acceptable quantity of the new crystalline form of 1-(((1(R)-
(3-(2-(7-chloro-2-quinolinyl)ethenyl)-phenyl)-3-(2-(1-hydroxy-1-methylethyl)phenyl)
10 propyl)thio)methyl) cyclopropane acetic acid of the present invention administered varies, dependent on the selected compound, the mode of administration, treatment conditions, age and status of the patient or animal species, and is subject to the final decision of the physician, clinician or veterinary doctor monitoring the course of treatment.

 Suitable oral and parenteral doses may vary within the range of from about 14.5
15 to about 286 µg per kg of body weight per day, preferably from about 29 to about 214 µg per kg of body weight and more preferably from about 58 to about 143 µg per kg of body weight per day. The new crystalline form of 1-(((1(R)-3-(2-(7-chloro-2-quinolinyl)ethenyl)-phenyl)-3-(2-(1-hydroxy-1-methylethyl)phenyl)propyl)thio)methyl) cyclopropane acetic acid may be formulated in a single dosage form that contains from about 1 to about 20 mg, preferably from
20 about 2 to about 15 mg, and more desirably from about 4 to about 10 mg of the active substance per unit dose.

Examples

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The following Examples illustrate the invention, but are not limiting.

Example 1 - Preparation of the Crystalline Form

1-(((1(R)-(3-(2-(7-chloro-2-quinoliny)ethenyl)-phenyl)-3-(2-(1-hydroxy-1-methylethyl) phenyl)propyl)thio) methyl)cyclopropane acetic acid (1 g) was suspended in
5 acetone (100 ml) and citric buffer pH=5 (100 ml). The suspension was sonicated in an
ultrasound bath at a temperature of 20 °C for 3 minutes. The precipitate formed after 24 h.
The crystals were filtered off and dried at room temperature under atmospheric pressure to
constant weight to give 0.85 g of the crystal form of 1-(((1(R)-(3-(2-(7-chloro-2-
quinoliny)ethenyl)-phenyl)-3-(2-(1-hydroxy-1-methylethyl)phenyl)propyl)thio)
10 methyl)cyclopropane acetic acid).

* * *

The present invention is not to be limited in scope by the specific embodiments
15 described herein. Various modifications of the invention in addition to those described herein
will become apparent to those skilled in the art from the foregoing description. Such
modifications are intended to fall within the scope of the appended claims.

All patents, applications, publications, test methods, literature, and other
materials cited herein are hereby incorporated by reference.

WHAT IS CLAIMED IS:

5 characteristic X-ray powder diffraction peaks, designated by 2θ and expressed in degrees, at $6.5\pm0.2^\circ$, $10.0\pm0.2^\circ$, $15.5\pm0.2^\circ$, $18.3\pm0.2^\circ$, $20.4\pm0.2^\circ$ and $24.6\pm0.2^\circ$.

10 the monoclinic space group $P 2_1$, and displaying unit cell parameters comprising:

crystal axis lengths of $a = 7.95(1)$ Å, $b = 21.94(1)$ Å, $c = 17.95(1)$ Å and an angle between the crystal axes of $\beta = 100.03(1)^\circ$.

15 quinoliny)ethenyl)-phenyl)-3-(2-(1-hydroxy-1-methylethyl)phenyl)
propyl)thio)methyl)cyclopropane acetic acid of claim 1 or claim 2, comprising

(i) dissolving 1-(((1(R)-3-(2-(7-chloro-2-quinolinyl)ethenyl)-phenyl)-3-(2-(1-hydroxy-1-methylethyl)phenyl) propyl)thio)methyl)cyclopropane acetic acid, or a salt thereof, in a mixture of acetone and one or more aqueous buffers, and

(ii) recrystallizing the 1-(((1(R)-(3-(2-(7-chloro-2-quinolinyl)ethenyl)-phenyl)-3-(2-(1-hydroxy-1-methylethyl)phenyl) propyl)thio)methyl)cyclopropane acetic acid.

4. The process of claim 3, wherein the ratio of one or more aqueous buffers to acetone is from about 1:5 to about 5:1.

5. The process of claim 3, wherein the crystallization step is performed at a pH of about 5 to about 8.

6. The process of claim 3, wherein recrystallization is performed at a temperature of from about 5 °C to about 50 °C.

10 7. The process of claim 3, further comprising

(iii) isolating the crystalline 1-(((1(R)-(3-(2-(7-chloro-2-quinolinyl)ethenyl)-phenyl)-3-(2-(1-hydroxy-1-methylethyl)phenyl) propyl)thio)methyl)cyclopropane acetic acid.

15 8. Crystalline 1-(((1(R)-(3-(2-(7-chloro-2-quinolinyl)ethenyl)-phenyl)-3-(2-(1-hydroxy-1-methylethyl)phenyl) propyl)thio)methyl)cyclopropane acetic acid prepared by the process of claim 3.

9. The crystalline 1-(((1(R)-(3-(2-(7-chloro-2-quinolinyl)ethenyl)-phenyl)-3-(2-(1-hydroxy-1-methylethyl)phenyl) propyl)thio)methyl)cyclopropane acetic acid of claim 1 or claim 20 2, having a purity of greater than about 90.0%.

10. The crystalline 1-(((1(R)-(3-(2-(7-chloro-2-quinolinyl)ethenyl)-phenyl)-3-(2-(1-hydroxy-1-methylethyl)phenyl) propyl)thio)methyl)cyclopropane acetic acid of claim 1 or claim 2, having a purity of greater than about 95.0%.

5 11. The crystalline 1-(((1(R)-(3-(2-(7-chloro-2-quinolinyl)ethenyl)-phenyl)-3-(2-(1-hydroxy-1-methylethyl)phenyl) propyl)thio)methyl)cyclopropane acetic acid of claim 1 or claim 2, having a purity of greater than about 99.0%.

10 12. The crystalline 1-(((1(R)-(3-(2-(7-chloro-2-quinolinyl)ethenyl)-phenyl)-3-(2-(1-hydroxy-1-methylethyl)phenyl) propyl)thio)methyl)cyclopropane acetic acid of claim 1 or claim 2, having a purity of greater than about 99.9%.

13. A pharmaceutical composition comprising the crystalline 1-(((1(R)-(3-(2-(7-chloro-2-quinolinyl)ethenyl)-phenyl)-3-(2-(1-hydroxy-1-methylethyl)phenyl)propyl)thio)methyl) cyclopropane acetic acid according to claim 1 or claim 2, and one or more pharmaceutically acceptable carriers or excipients.

15

14. A method of treating asthma in a human which comprises administering to a patient in need of such treatment an effective amount of the crystalline form of 1-(((1(R)-(3-(2-(7-chloro-2-quinolinyl)ethenyl)-phenyl)-3-(2-(1-hydroxy-1-methylethyl)phenyl)propyl)thio)methyl) cyclopropane acetic acid of claim 1 or claim 2.

20

ABSTRACT

The present invention relates to a new crystalline form of 1-(((1(R)-3-(2-(7-chloro-2-quinolinyloxy)ethoxy)-phenyl)-3-(2-(1-hydroxy-1-methylethoxy)phenyl)propyl)thio)methyl)cyclopropane acetic acid, to a process for its preparation, to pharmaceutical formulations
5 containing it, and to a method of treatment using the same

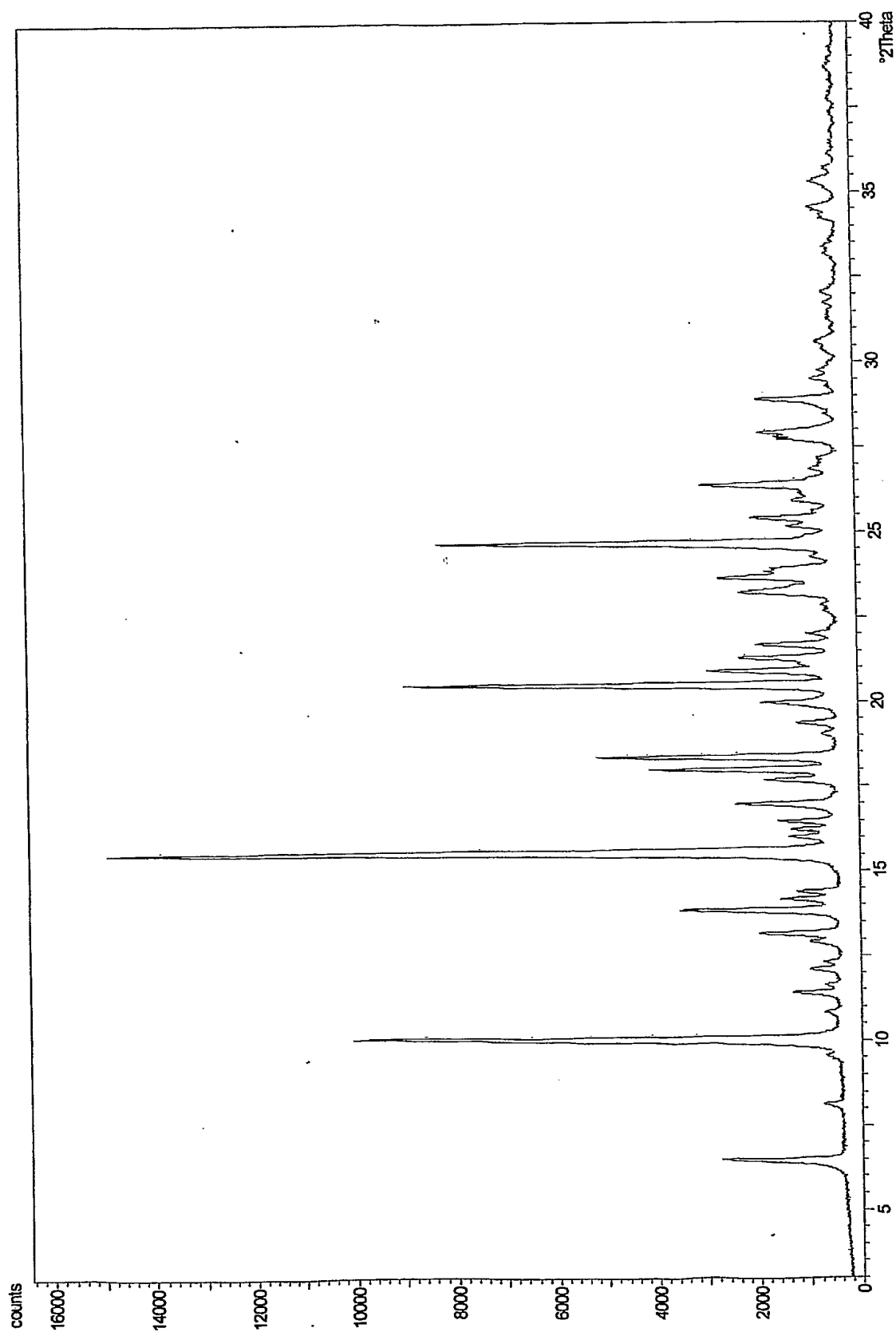


Figure 1.

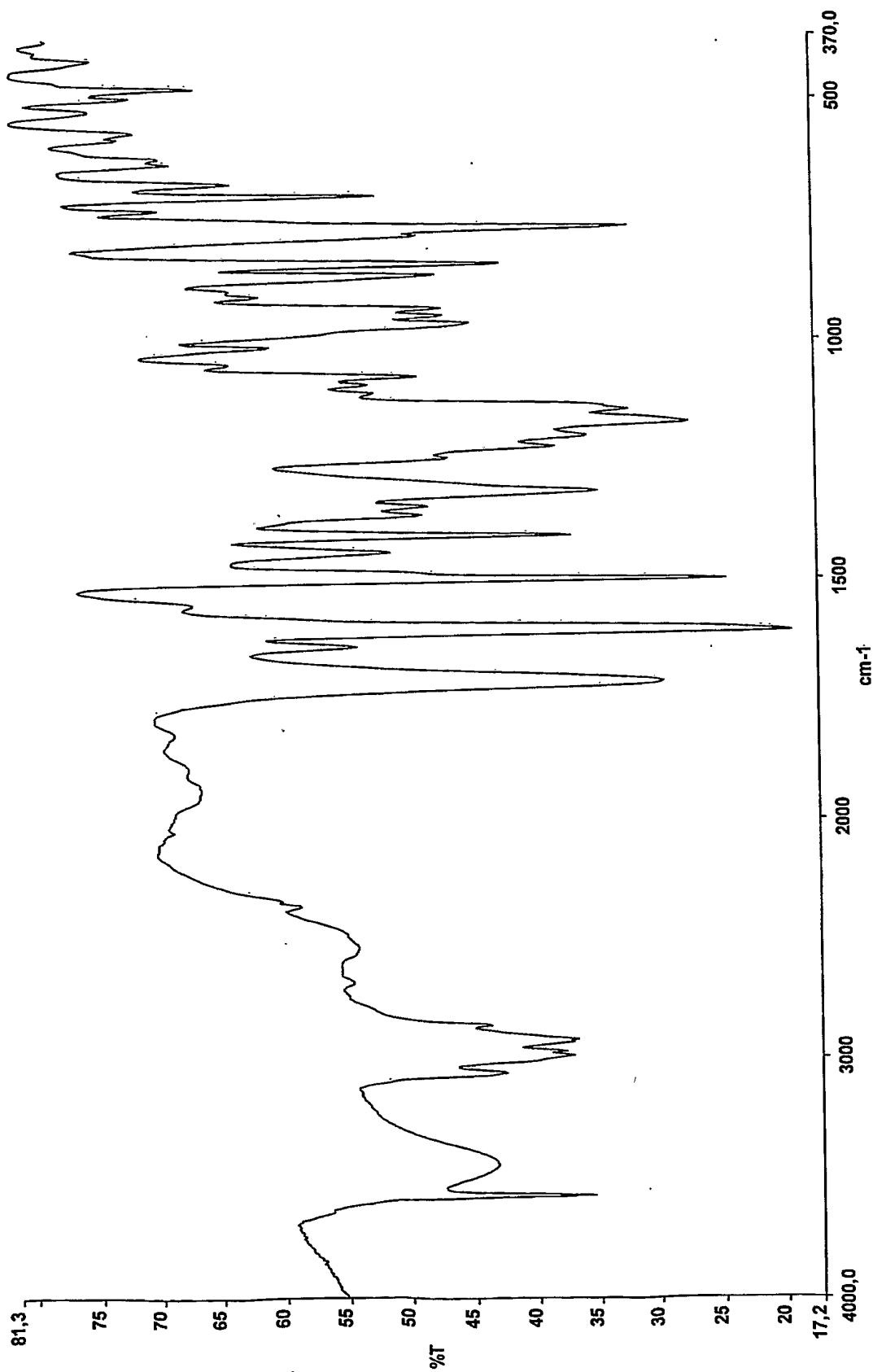


Figure 2.

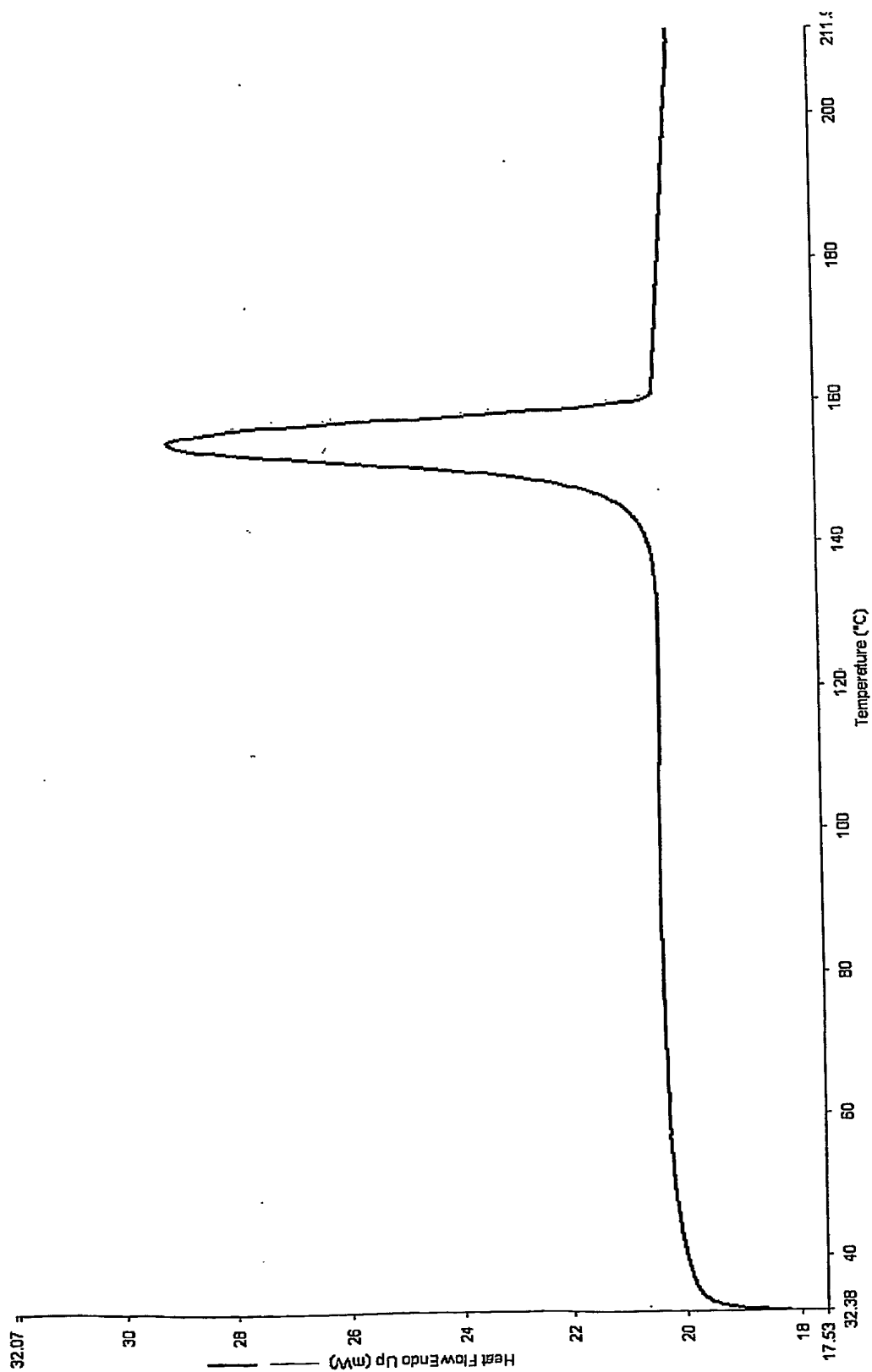


Figure 3.